

Associations Between Prematurity, Birthweight, and Adolescence Blood Pressure in a Nationwide Cohort



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Introduction: Prematurity is associated with incomplete nephrogenesis and an increased incidence of acute kidney injury, that may increase the risk of future kidney disease, including hypertension, proteinuria and reduced glomerular filtration rate. The aim of this study was to evaluate the risk of hypertension or proteinuria in adolescents born prematurely or small for gestational age, in a nationwide cohort.

Methods: The study cohort included potential recruits examined in the Israel Defense Forces (IDF) medical facilities, between November 2005 and October 2018. Clinical and anthropometric data, including blood pressure (BP) measurement, were retrieved from the IDF medical files. Adolescents born between January 1993 and December 2000 had additional data on gestational age at birth, retrieved from the Israeli Ministry of Health database.

Results: The study cohort included 513,802 participants, aged 17.3 ± 0.9 years, of whom 48,994 had gestational age data. Adolescents born as very preterm, as extremely preterm infants, those born with very low birthweight (VLBW), or with extremely low birthweight (ELBW) had higher incidence of hypertensive-range BP (55%, 47%, 19% and 12%, respectively). No significant association between birthweight (BW) adjusted to gestational age and hypertension was observed. Within the overweight and obese adolescents, those born with VLBW and ELBW, had further increased hypertensive-range BP rate. Proteinuria was diagnosed in 0.33% of the study cohort, with no significant difference between BW or gestational age categories.

Conclusion: Adolescents born with VLBW or as significant preterm were associated with high BP and should be monitored for hypertension development and its potential complications.

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KEYWORDS: acute kidney injury; adolescent hypertension; birthweight; chronic kidney disease; prematurity; proteinuria

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Prematurity is a global phenomenon with 15 million infants born preterm annually, and an estimated 11% of total deliveries ending prematurely.¹ During the past decades, major improvements in neonatal care have led to improved survival of premature infants. Moreover, long-term complications, including an increased risk for chronic kidney disease (CKD), remain significant.²

Nephrogenesis is not complete in premature infants, because 60% of the nephrons are formed during the

second half of gestation, with completion of new nephron formation between 32 and 36 weeks gestation.^{3,4} Therefore, the final nephron number that is variable, ranging from 200,000 to 2.5 million nephrons,⁵ can be reduced. Premature infants are also at high risk of developing acute kidney injury (AKI) episodes. Adaptive kidney mechanisms that initially preserve kidney function may become destructive later in life, by causing intraglomerular hypertension, which leads to glomerular sclerosis and further diminishes nephron population.⁶ Therefore, premature infants with incomplete nephrogenesis and AKI episodes may be prone to CKD. Previous studies reported higher prevalence of CKD manifesting as proteinuria and low glomerular filtration rate (GFR) in LBW infants in comparison to their normal BW counterparts.^{7–9}

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Our study's hypothesis is that adolescents born prematurely or small for gestational age (SGA) will have higher BP measurements in comparison to term infants with normal BW. The current study explores this hypothesis in late adolescents, aged 16 to 18 years, in a large nationwide Israeli cohort.

METHODS

All Israeli adolescents who are eligible for compulsory military service undergo medical examination to assess their health status. This assessment includes a primary care medical report, a comprehensive medical history and a thorough physical examination, including measurements of weight, height, urinalysis test, and BP. BP is measured twice after 5 to 10 minutes of rest in the sitting position with an appropriately sized cuff on the right arm, using a manual aneroid sphygmomanometer. The recorded BP reflects the average of 2 consecutive measurements taken at the same occasion.

The study population included potential recruits that were examined in an IDF medical facility between November 2005 and October 2018.

For each individual, data on sex, date of birth, BW, weight, height, and BP at time of examination, as well as medical background, were retrieved from the IDF electronic medical system. Out of the study cohort, adolescents born between January 1993 and December 2000 had data on gestational age at birth that were retrieved from the Israeli Ministry of Health database.

The study population was categorized into 5 groups according to BWs: normal BW (2500–3999 g), LBW (1500–2499 g), VLBW (1000–1500 g), ELBW (<1000 g), and high BW (>4000 g).

Gestational age at delivery was categorized into 4 subgroups according to the World Health Organization classification: term (37 weeks, 0 days and later), late and moderate preterm (32 weeks, 0 days to 36 weeks, 6 days), very preterm (28 weeks, 0 days to 31 weeks, 6 days) and extremely preterm (<27 weeks, 6 days). We then divided each group into BW categories as follows: SGA (BW below the 10th percentile for gestational age), appropriate for gestational age (AGA, BW between 10th and 90th percentile for gestational age), and large for gestational age (LGA, BW above 90th percentile for gestational age) according to the Dollberg birth scales.¹⁰

Individuals with any diagnosis suggesting possible future risk for CKD such as congenital anomalies of the kidneys and urinary tract, glomerular disease, cystic kidney disease, hematuria, urolithiasis, diabetes mellitus, tumors and lymphoproliferative diseases, kidney transplant, or bone marrow transplant were excluded

from this study. Individuals with missing records were excluded from the study.

Body mass index (BMI) was calculated as weight (in kg) divided by the squared height (in m). Subgroups of BMI for the study cohort were defined according to the 2000 US Centers for Disease Control and Prevention BMI for age and sex classification of children and adolescents as follows: (i) underweight was considered as a BMI below the fifth percentile (14.00–17.70 for boys and 14.00–17.20 for girls), (ii) normal weight was considered as a BMI between the fifth and 84th percentiles (17.71–24.89 for boys and 17.21–25.19 for girls), (iii) overweight was considered as a BMI between the 85th and 94th percentiles (24.90–28.19 for boys and 25.20–29.59 for girls), (iv) obesity was considered as a BMI at or exceeding the 95th percentile (28.20–40.00 for boys and 29.60–40.00 for girls).

The American Heart Association categories were used to determine BP stage. Therefore, normal BP was considered as systolic BP of less than 120 mm Hg with diastolic BP of less than 80 mm Hg. Elevated BP was considered as systolic BP of 120 to 129 mm Hg with diastolic BP of 80 mm Hg and below. Stage 1 hypertension was considered as systolic BP of 130 to 139 mm Hg or diastolic BP of 80 to 89 mm Hg. Stage 2 hypertension was considered as systolic BP of 140 mm Hg and higher or diastolic BP of 90 mm Hg and higher.

During statistical analysis, that was done using IBM SPSS statistics software package (IBM Corp, Armonk, NY), both grades 1 and 2 were classified as having hypertension, whereas elevated and normal BP were classified as not having hypertension. Given that BP was measured on a single medical visit, and not on 3 separate visits as recommended, we used the term hypertensive-range BP (either stage 1 or 2) and not simply hypertension.

Proteinuria, retrieved from the IDF medical files, was defined as a positive dipstick, followed by 24-hour urine protein excretion exceeding 200 mg.

Continuous variables were presented as average and SD and categorical variables as prevalence and percentage. The association between prematurity, BW, and CKD manifestations were analyzed using chi-square test and logistic regression models.

Ethical approval for the study was provided by the IDF Medical Corps Institutional Review Board, which waived the need for informed consent based on the strict maintenance of participants' anonymity.

RESULTS

The entire cohort comprised 523,593 adolescents, of whom 9791 were excluded due to past medical

conditions possibly related to CKD, as described earlier, as presented in Figure 1. Thus, 513,802 participants, aged 17.3 ± 0.9 years, were included in our study; 302,002 (58.8%) were male and 489,638 (95.3%) were Jewish (Table 1).

Of the study population, 97% (496,121 individuals) had reliable BP measurements. Forty-six percent (226,774 individuals) had normal BP, 22% (109,924) had elevated BP, 27% (132,179) had stage 1 hypertensive-range BP, and 5.5% (27,244) had stage 2 hypertensive-range BP at the time of examination.

Hypertensive-Range BP and Gestational Age at Birth

Of the study population, 46,642 individuals (9.1% of the entire study cohort) had data on gestational age at birth (38.8 ± 2.99 weeks in average). The prevalence of hypertensive-range BP in this subgroup was slightly lower than in the entire cohort (28.6% vs. 32.1%, respectively). Gestational age category was found to be significantly associated with hypertensive-range BP ($P < 0.001$) Odds ratios (ORs) and confidence intervals (CIs) are presented in Table 2.

Hypertensive-Range BP and BW

Of the study population, 417,682 individuals (81.3%) had registered BW and BP measurements. The prevalence of hypertensive-range BP in each BW subgroup is

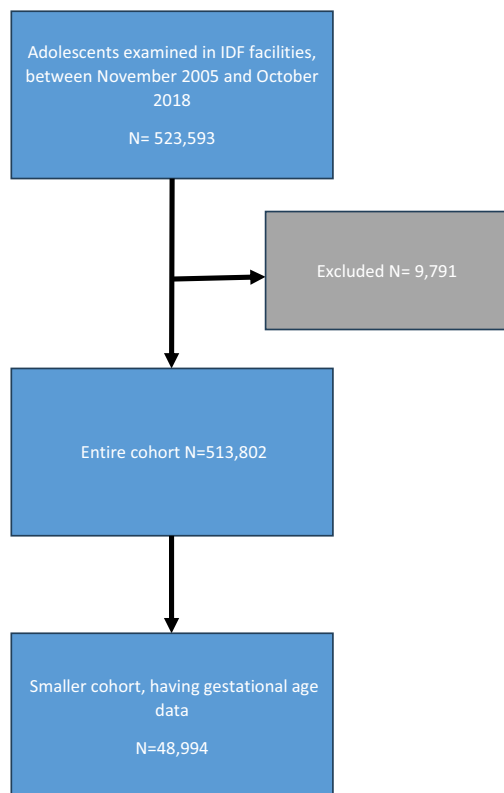


Figure 1. Consort flow diagram of study participants. IDF, Israel Defense Forces.

Table 1. Study participants' characteristics

Participant's characteristics	Male	Female
Number of participants, <i>n</i> (%)	302,002 (58.8)	211,800 (41.2)
BP ^a (mm Hg)	123 ± 12 / 69 ± 9	114 ± 12 / 69 ± 8
% With hypertensive-range BP, <i>n</i> (%)	117,995 (41)	41,428 (20)
Weight ^a (kg)	69.2 ± 14.8	59.0 ± 12.4
Height ^a (cm)	173.9 ± 6.8	161.9 ± 6.2
BMI ^a (kg/m ²)	22.5 ± 4.4	22.1 ± 4.2

BMI, body mass index; BP, blood pressure.
^aAverage ± standard deviation.

presented in Table 2 and Figure 2. We found a significant difference in the prevalence of hypertensive-range BP between the different BW categories ($P < 0.001$). ORs and CIs are presented in Table 2.

The cohort of 48,994 individuals whose gestational age at delivery was documented, was divided into gestational age subgroups (term, moderate and late preterm, very preterm, and extremely preterm). We then divided each group into BW categories (SGA, AGA, and LGA) as formerly described. There was no significant difference in the prevalence of hypertensive-range BP between different BWs within each gestational age category as depicted in Table 3.

BMI and Hypertensive-Range BP

BMI values were classified into 4 categories (normal, underweight, overweight, and obese). We found a significant difference in the prevalence of hypertensive-range BP between the categories ($P < 0.001$). Comparing hypertensive-range BP in the overweight and obese groups with the normal BMI group showed increased hypertensive-range BP prevalence,

Table 2. Prevalence of hypertensive-range BP in the different gestational age categories (moderate and late preterm, very preterm, and extremely preterm groups compared to term group [Ref^a], ($P < 0.001$) and in different birthweight groups (LBW, VLBW, ELBW and high birthweight compared to normal birthweight [Ref^b], [$P < 0.001$])

Gestational age and birth weight groups	Hypertensive-range BP, <i>n</i> (%)	Odds ratio (CI)
Gestational age groups		
Term (<i>n</i> = 40,944)	11,431 (27.9)	Ref ^a
Moderate and late preterm (<i>n</i> = 3699)	1,139 (30.8)	1.14 (1.07–1.23)
Very preterm (<i>n</i> = 1222)	459 (37.6)	1.55 (1.35–1.75)
Extremely preterm (<i>n</i> = 777)	283 (36.4)	1.47 (1.28–1.71)
Birthweight groups		
Normal BW (<i>n</i> = 359,838)	116,108 (32.3)	Ref ^b
LBW (<i>n</i> = 30,886)	9780 (31.7)	0.97 (0.95–1)
VLBW (<i>n</i> = 2725)	987 (36.2)	1.19 (1.1–1.29)
ELBW (<i>n</i> = 865)	300 (34.7)	1.12 (0.97–1.28)
High BW (<i>n</i> = 150,619)	135,941 (37.4)	1.25 (1.22–1.29)

BW, birthweight, CI, confidence interval; ELBW, extremely low birthweight; LBW, low birthweight; VLBW, very low birthweight; Ref, reference.

^aRef-term gestational age group.

^bRef-normal birth weight group.

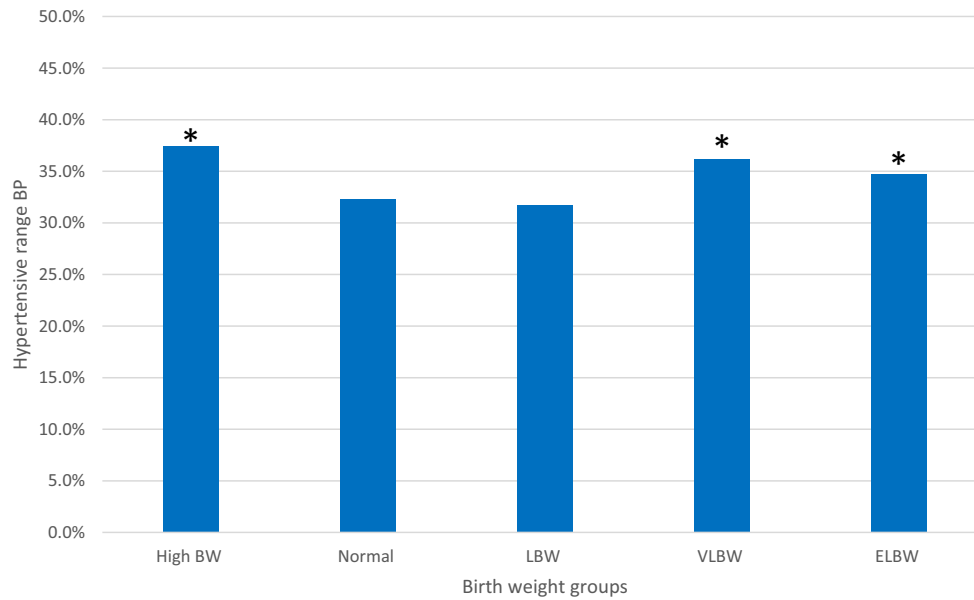


Figure 2. Prevalence of hypertensive-range BP in different birthweight groups (normal, LBW, VLBW, ELBW, and high BW). BP, blood pressure; BW, birthweight; ELBW, extremely low birthweight; LBW, low birthweight; VLBW, very low birthweight. *Statistically significant difference from normal BW, $P < 0.001$.

with an OR of 1.75 (95% CI: 1.72–1.78) and 3.15 (3.07–3.23), respectively. The underweight BMI group showed decreased prevalence of hypertensive-range BP in comparison to normal BMI group with an OR of 0.67 (95% CI: 0.66–0.69). Each of the 5 BW subgroups (normal, LBW, VLBW, ELBW, and high BW) was divided into 4 BMI subgroups, as presented in Figure 3. We found a significant difference in the prevalence of hypertensive-range BP between BW groups within each BMI category.

In a model adjusted for BMI, all BW groups except LBW, had a significant effect on hypertensive-range BP, with an OR of 1.29 (95% CI: 1.19–1.29), 1.25 (95% CI: 1.09–1.44) and 1.15 (95% CI: 1.12–1.18) for VLBW, ELBW, and high BW, respectively, compared to normal BW.

A multivariate analysis of the entire cohort ($N = 513,802$), including sex, BW groups, and BMI subgroups variables, revealed that the most powerful

predictors for hypertensive-range BP were male sex, VLBW and ELBW, and overweight and obese BMI (Figure 4).

A second multivariate analysis in the smaller cohort ($n = 48,994$), including sex, BW groups, gestational age groups, and BMI categories variables, showed similar predictors for hypertensive-range BP with the addition of very preterm (but not extremely preterm) infants (Figure 5).

Proteinuria

Proteinuria was found in 1684 (0.33%) of the study population with no significant difference between BW categories (normal, LBW, VLBW, ELBW, high BW) ($P = 0.44$). Among participants with recorded gestational age ($n = 48,994$), there was a significant difference between the 3 BW-according-to-gestational-age groups (SGA, AGA, and LGA) in the prevalence of proteinuria ($P = 0.04$). Only LGA had a higher prevalence of proteinuria than the AGA group (OR 2, 95% CI: 1.12–3.58). There was no significant difference in the prevalence of proteinuria between the different gestational age categories (term, late and moderate preterm, very preterm, and extremely preterm).

Table 3. Prevalence of hypertensive-range BP within each gestational age group between different weight groups

Gestational age groups	SGA, %, (n) ^a	AGA, % (n) ^a	LGA, % (n) ^a	Comparison between SGA,
				AGA, LGA (P-value) ^a
Term	27.6 (1127)	27.9 (9191)	28.8 (1113)	0.424
Moderate and late preterm	30.0 (268)	31.4 (818)	26.4 (53)	0.273
Very preterm	37.8 (48)	37.4 (401)	43.5 (10)	0.836
Extremely preterm	30.3 (10)	36.5 (255)	39.1 (18)	0.711

AGA, appropriate for gestational age; LGA, large for gestational age; SGA, small for gestational age.

^aBirthweight adjusted to gestational age groups.

DISCUSSION

In this large nationwide population-based study, very and extremely preterm as well as VLBW and ELBW were found to be significantly associated with adolescent hypertensive-range BP. Adolescents born as very and extremely preterm infants had 55% and 47% greater risk of having hypertensive-range BP,

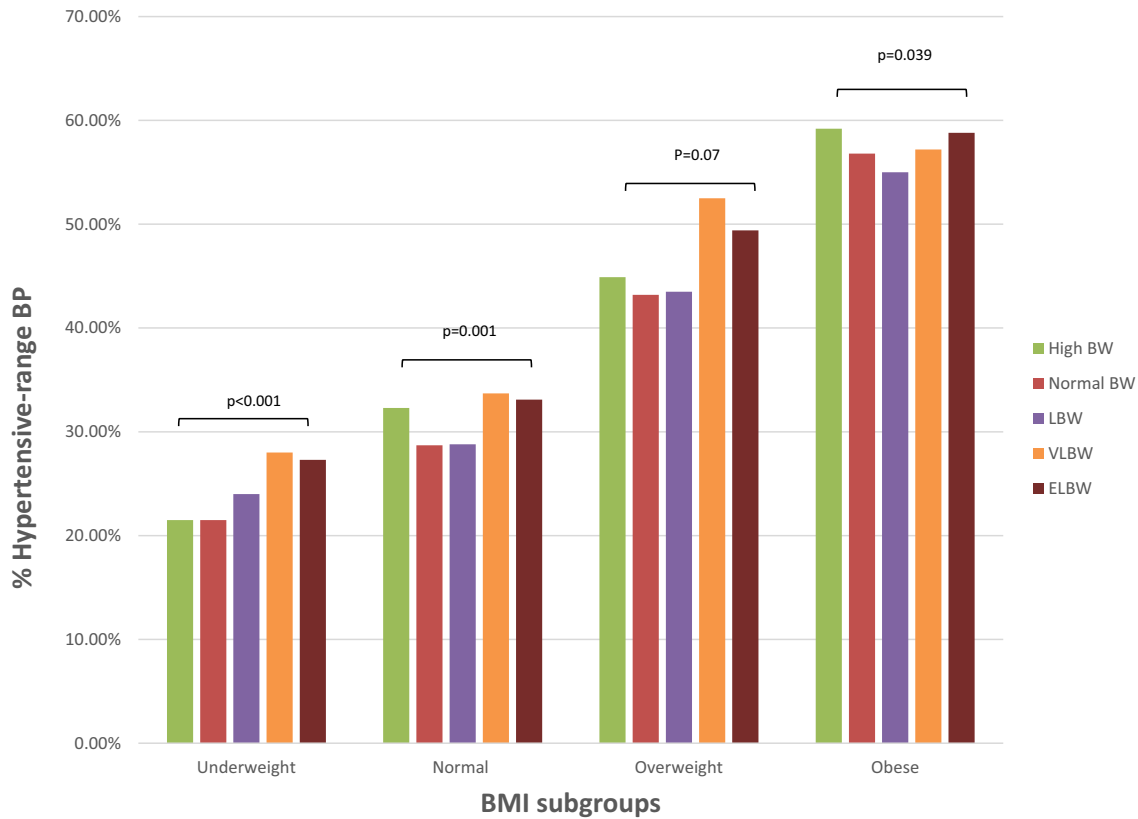


Figure 3. Prevalence of hypertensive-range BP in different birthweight groups (normal, LBW, VLBW, ELBW, and high BW) according to BMI subgroups (underweight, normal, overweight, and obese). BMI, body mass index; BW, birthweight; ELBW, extremely low birthweight; LBW, low birthweight; VLBW, very low birthweight.

respectively. Being born with VLBW or ELBW increased the risk of adolescent hypertensive-range BP by 19% and 12%, respectively. Low BW can be either due to prematurity or intrauterine growth retardation that resulted in SGA in a term infant. In our cohort, we found no significant association between BW adjusted to gestational age and hypertensive-range BP within

each specific gestational age category, which may imply that prematurity is a stronger predictor of hypertension than BW alone.

Adolescent hypertensive-range BP was 25% higher in participants born LGA. Adolescents who are currently overweight or obese had a 1.75-fold and 3.15-fold higher prevalence of hypertensive-range BP,

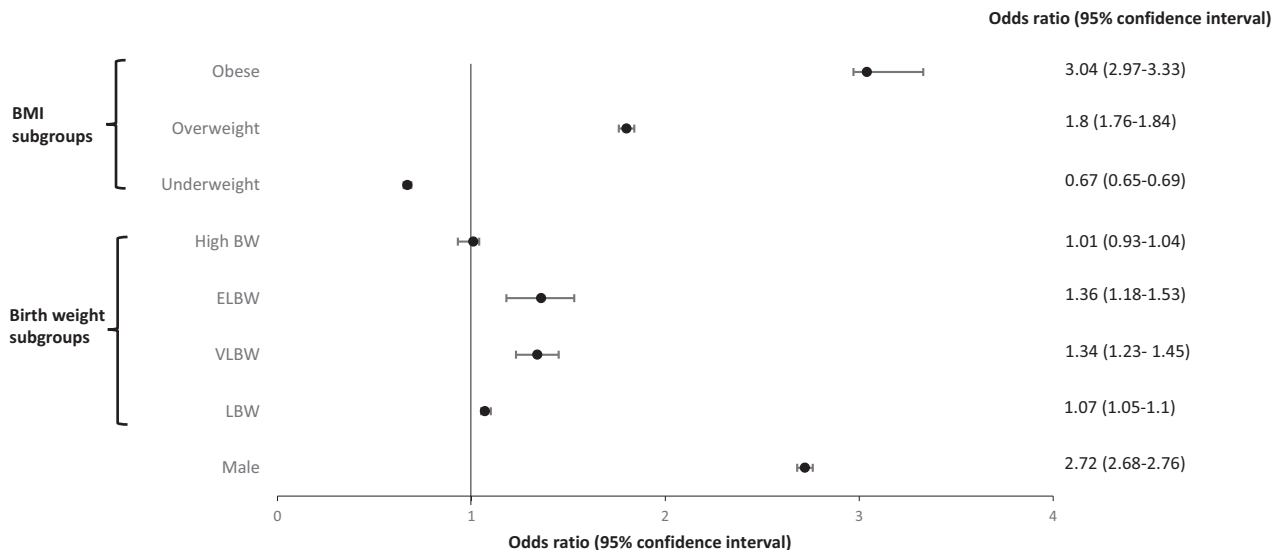


Figure 4. Predictors of hypertensive-range BP in the entire cohort (N = 513,802) presented as odds ratio and 95% confidence interval. ELBW, extremely low birthweight; LBW, low birthweight; VLBW, very low birthweight.

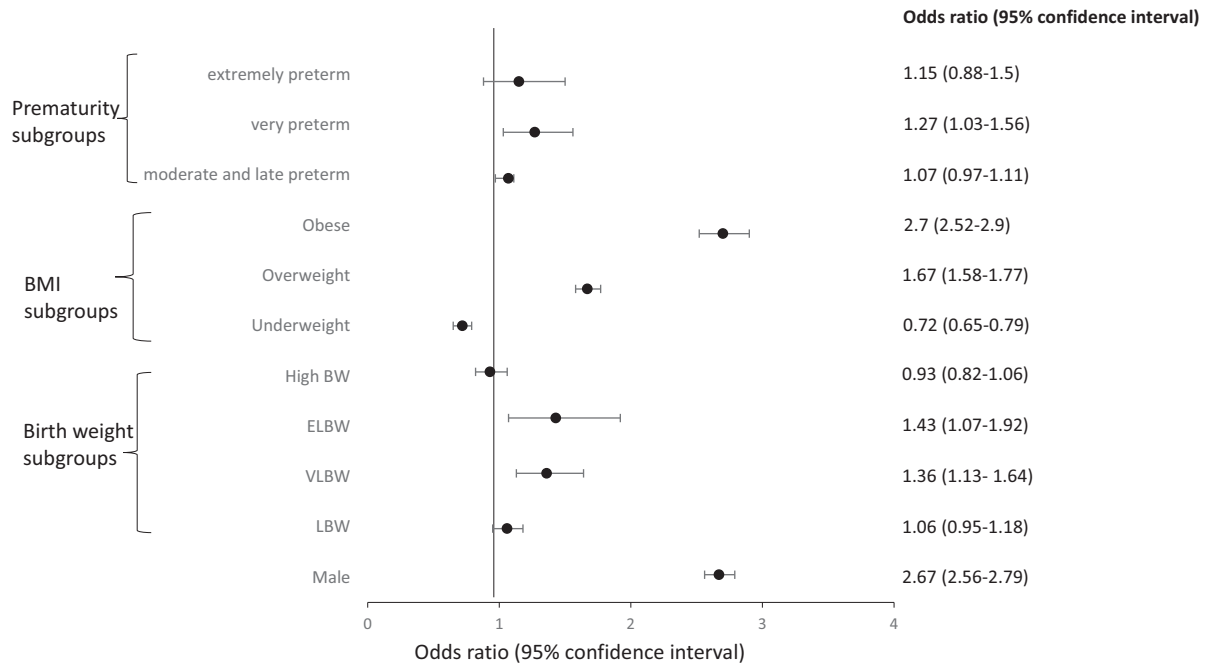


Figure 5. Predictors of hypertensive-range BP in the smaller cohort ($n = 48,994$) presented as odds ratio and 95% confidence interval. BW, birthweight; ELBW, extremely low birthweight; LBW, low birthweight, VLBW, very low birthweight; ELBW, extremely low birthweight.

respectively. Within the overweight and obese adolescents, those born as VLBW and ELBW, had further increased hypertensive-range BP rate compared to those born with normal BW.

Proteinuria was uncommon in our cohort, diagnosed in only 0.33% of the entire cohort. It was found to be significantly higher only among the LGA group (twice higher risk than the AGA group). The lower prevalence of proteinuria might have prevented us from identifying additional significant predictors of proteinuria. Because of the retrospective nature of our study, mild proteinuria might have been overlooked.

Nephrogenesis begins in the ninth week and completes between the 32nd and 36th weeks of gestation,³ with the majority of the nephrons formed in the third trimester of pregnancy.⁴ Although nephrogenesis may continue in premature infants for up to 40 days after birth, these nephrons are abnormal and age at an accelerated rate.¹¹ According to Brenner's hyperfiltration theory, decreased nephron endowment causes glomerular hypertrophy, which initially maintains GFR in the normal range. Overtime, adaptive mechanisms may become destructive by causing intraglomerular hypertension, which leads to glomerular sclerosis and further diminishes nephron population. As this process continues, reduction in GFR is inevitable.⁶ Therefore, the number of nephrons an individual possesses at birth will impact their future risk for developing CKD. Premature infants are also at high risk of developing AKI episodes secondary to birth asphyxia, sepsis, patent ductus arteriosus, and hypotension leading to

renal hypoperfusion as well as infections, and nephrotoxic drugs. Jetton *et al.* reported AKI incidence of 30% in over 2000 infants admitted to neonatal intensive care units, and an increased risk of 47.9% incidence of AKI in preterm infants born at less than 29 gestational weeks.¹² An even higher AKI incidence rate of 56% in ELBW neonates was demonstrated.¹³ Therefore, premature infants with either incomplete nephrogenesis and AKI episodes are prone to CKD.

A meta-analysis by White *et al.* that included more than 2 million individuals from 31 studies, demonstrated an 80% increased risk of both albuminuria and sustained low GFR and 60% increased risk of kidney failure later in life in LBW, compared to their normal BW counterparts.⁷ In a study by Gjerde *et al.* in Norway, that included 2,663,010 individuals with a mean follow up of 26 years, 4495 had been diagnosed with CKD. Compared to participants born at term with a normal BW, the odds ratio for developing CKD was 1.73, 1.79 and 1.48 for LBW, SGA, and preterm birth, respectively.⁸ Another national cohort study in Sweden by Crump *et al.*, of 4,186,615 singleton live births described 2- to 3-fold increased risk for developing CKD from childhood to midadulthood, in preterm (<37 weeks) and extremely preterm (<28 weeks), respectively.⁹

Hypertension diagnosis is usually based on BP measurements taken in at least 3 separate visits in both pediatric and adult populations.^{14,15} Using repeated BP measurements for diagnosis, adolescent's hypertension and prehypertension prevalence is reported to be

between 3.2% and 15.7%, respectively. Higher prevalence of combined prehypertension and hypertension, among obese adolescents, was detected in over 30% of males and 23% to 30% of females.¹⁶ Different prevalence was reported in different populations; 2% to 20.5% in different studies in India,¹⁷ 8% in a meta-analysis from Brazil.¹⁸ In our study, hypertensive-range BP diagnosis based on a single visit twice measured BP, was found in a higher prevalence of 26.6% having stage 1 hypertensive-range BP and 5.5% having stage 2 hypertensive-range BP. Similar findings were reported for adolescents and young adults (age 18–39 years) by Zhang *et al.* in the NHANES study, in which a similar single visit BP measurement was performed. The study showed that the prevalence of combined prehypertension and stage 1 hypertension was 23.4% and stage 2 hypertension was 7.3%.¹⁹ Although the diagnosis of hypertension should be based on repeated measurements, our findings show a definite trend of high BP among adolescents born as VLBW and ELBW infants and as very and extremely preterm newborns.

Another significant finding of our study was the difference in the BP measurements between males and females; 19.9% of females had measurements consistent with the definition of hypertensive-range BP, in comparison to 41% of males ($P < 0.001$). A milder difference in hypertension prevalence between sexes was reported in a meta-analysis by De Moaes *et al.*, showing pooled prevalence of high BP of 11.2%, 13% in males, and 9.6% in females.²⁰

The significant difference in the prevalence of hypertensive-range BP between males and females seen in our study, may arise from the criteria used for hypertension diagnosis. In our study, BP was diagnosed according to the American Heart Association classification as recommended by current guidelines for age 13 and above.¹⁵ The American Heart Association BP thresholds are the same for both sexes. BP percentiles in children are based on sex, age, and height; with lower values for girls. Defining hypertension as BP percentile over 95th percentile might have increased the prevalence of hypertension in females in our study.

Adolescents who are overweight or obese are more likely to develop hypertension. Given the increasing prevalence of obesity in high-income countries and its various health implications, including future kidney disease as reported by Twig *et al.*,²¹ this finding is also important and concerning. Hypertension is a well-known risk factor for future cardiovascular disease. As previously described by Leiba *et al.* adolescent hypertension, especially in overweight and obese adolescents, is associated with cardiovascular mortality in young and midadulthood.²²

Many previous studies describing the association between LBW and hypertension did not consider gestational age. LBW may represent either prematurity or intrauterine growth restriction. A recent genome-wide association study suggested a genetic etiology for the inverse association between BW and subsequent hypertension in term infants.²³ In an analysis of the subgroup with known gestational age in our study, only prematurity, and not BW *per se*, was associated with the risk of hypertension. This might imply a different etiology, that is, reduced nephron endowment, for adolescent hypertension in premature infants.

This study's main limitation is relying on 2 BP measurements performed in a single visit. We decided not to consider other documented BP measurements taken during the military service because they were recorded during illnesses and not routinely, which may have influenced the credibility of the results. Another limitation is that we had gestational age information in only 9.1% of the entire cohort. It should also be noted that most of study participants are Jewish, male adolescents. In Israel, military service is mandatory for Jewish male adolescents whereas female adolescents can volunteer to national service instead. Arab adolescents are not obligated to enlist in the army. In addition, adolescents with significant medical conditions, that are common in severe premature infants, are automatically exempt from military service, and are therefore not represented in our cohort. Therefore, our findings might be an underestimation of the true prevalence of hypertension in adolescents born prematurely.

In conclusion, our study demonstrated a trend for hypertension in very premature infants and in infants born with VLBW and ELBW. Hypertension and proteinuria can be early manifestations of CKD. Those results suggest that adolescents born prematurely or very small should be carefully monitored for hypertension, proteinuria, or low GFR in order to treat disease manifestation and hopefully delay disease progression and cardiovascular disease. Further studies are needed to evaluate long-term CKD manifestations of prematurity.

DISCLOSURE

All the authors declared no competing interests.

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